

WO 03/087842

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Claims

1. A method for the identification/isolation  
of modulators of a secretase activity wherein  
suitable eukaryotic host cells are contacted  
with a test substance wherein said suitable host cells  
comprise:

- 10           a) a fusion protein comprising a secretory protein, a membrane anchor domain and a secretase cleavage sequence,

15           b) a protein comprising a secretase activity recognising said cleavage sequence of said fusion protein and

20           c) at least one reporter gene under control of a transcriptional activation system wherein said transcriptional activation system is regulated by the release of said secretory protein from said fusion protein by said secretase activity and its subsequent secretion

20 then culturing said cells under suitable conditions such that said reporter gene allowing detection and/or survival of cells is only expressed or repressed in a manner that is dependent on an altered secretase activity due to said test substance.

25                   2. Method for the isolation of a secretase  
inhibitor according to claim 1, wherein a reduced or no  
release of said secretory protein due to a reduced/ in-  
hibited secretase activity leads to expression of said at  
least one reporter gene thereby allowing detection and/or  
30 survival of cells under suitable culturing conditions.

3. Method according to claim 1 or 2, wherein  
said at least one reporter gene is selected from genes  
conferring antibiotic resistance, genes encoding reporter  
molecules with an activity that can be detected by col-  
35 orimetric or fluorescent methods and genes complementing  
auxotrophies, preferably a His3 gene.

WO 03/087842

PCT/IB02/01342

21

4. Method for the identification of agonists of a secretase activity according to claim 1, wherein the release of said secretory protein due to an enhanced secretase activity leads to a reduced expression of said at least one reporter gene thereby allowing detection and/or survival of cells under suitable conditions.

5. Method according to claim 4, wherein said at least one reporter gene is selected from genes conferring sensitivity to a chemical.

10 6. Method according to anyone of the preceding claims, wherein said cells comprise a second reporter gene selected from the group consisting of:

- 15 a) genes encoding reporter molecules with an activity that can be detected by colorimetric or fluorescent methods,  
b) genes conferring antibiotic resistance and genes conferring sensitivity to a chemical and  
c) genes complementing auxotrophies.

7. Method according to anyone of the preceding claims, wherein said cell is a yeast cell.

20 8. Method according to anyone of the preceding claims, wherein said secretory protein has an enzymatic activity, preferably a protein with invertase activity or functional fragments of a protein with invertase activity.

25 9. Method according to anyone of the preceding claims, wherein said secretory protein is a yeast invertase or functional fragments of a yeast invertase.

10. Method according to anyone of the preceding claims, wherein said secretase cleavage sequence is selected from the  $\beta$  site and the  $\alpha$  site of the human amyloid precursor protein and the S2 site of Notch 1 protein.

30 11. Method according to claim 10, wherein into said  $\beta$  site the Lys595Asn and Met596Leu changes were introduced.

WO 03/087842

PCT/IB02/01342

22

12. Method according to anyone of the preceding claims, wherein said fusion protein comprises an ER retention signal.

13. Method according to anyone of the preceding claims, wherein said fusion protein comprises amino acid residues 1-532 of yeast invertase, amino acid residues 590-695 of human APP and an ER retention signal.

14. Method according to anyone of the preceding claims, wherein said fusion protein comprises amino acid residues 1-532 of yeast invertase, amino acid residues 1714-1876 of human Notch 1 and an ER retention signal.

15. Method according to anyone of the preceding claims, wherein a nucleic acid construct encoding said fusion protein is integrated into the genome of said host cell.

16. Method according to anyone of the preceding claims, wherein said protein comprising a secretase activity recognising said cleavage sequence of said fusion protein further comprises an ER signal sequence.

17. Method according to anyone of the preceding claims, wherein said secretase activity is selected from  $\beta$ -secretase and  $\alpha$ -secretase.

18. Method according to claim 16, wherein said protein comprising a  $\beta$ -secretase activity further comprises an ER signal sequence and amino acid residues 616-695 of human APP.

19. Method according to anyone of the preceding claims, wherein said transcriptional activation system comprises at least part of the yeast GAL gene regulatory system.

20. Method according to anyone of the preceding claims, wherein said reporter gene is under control of the yeast GALL-10 regulatory region.